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Chapter 7

The Long-term Effects of Depot Antipsychotics or Clozapine on Sexual Functioning, Preliminary Results

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Summary

In a target population of about 200 patients treated with classical antipsychotics or clozapine for more than half a year 35 patients (21 classical, 14 clozapine) could be included in a cross-sectional study evaluating sexual side effects attributed to the treatment of antipsychotics. Libido reduction was reported in 33% of the patients in both treatment groups. There was a trend of less detrimental effects of clozapine on erections orgasm and ejaculation in comparison to classical antipsychotics. The sample-size of the study was small, the identified differences between the groups did not reach statistic significance. As the frequency of reported sexual dysfunctions in this long-term study are in line with reports in short-term studies, this studies supports the hypothesis that sexual side effects don't subside over time. Definite conclusions of clozapine inducing less sexual side effects than classical antipsychotics can't be drawn, due to the small sample-size and possible selection bias, but extending the study is warranted.

Introduction

The prevalence of sexual dysfunctions that are related to the use of antipsychotics is only infrequently. Only few studies have been published, estimating the prevalence of sexual dysfunctions between 25 and 60% in patients using antipsychotic drugs for six weeks (Knegtering et al. 2003). A few studies on the prevalence of sexual dysfunctions after long-term use ranging from six months to many years suggest that sexual side effects do not subside over time (Ghadirian et al. 1982; Lingjaerde et al. 1987). Although the relative burden of sexual dysfunctions is probably high it is only seldom investigated (Finn et al. 1990; Smith et al. 2002). In the literature sexual dysfunctions in patients with schizophrenia are often attributed to a combination of the disease process (schizophrenia) and the effects of antipsychotics (Knegtering et al. 2003). There are suggestions in the literature that prolactin-elevating antipsychotics are associated with more serious sexual dysfunctions in comparison to patients using prolactin sparing antipsychotics (Kim et al. 2002; Knegtering et al. 2002). In agreement with this literature is the study of Aizenberg who switched 30 out of 60 patients from classical antipsychotics to clozapine in a randomized study. Patients continuing treatment with classical antipsychotics reported more sexual side effects than patients switching to clozapine (Aizenberg et al. 2001).

This was in contrast to the findings of Hummer et al, who compared the effects on sexual functioning of haloperidol (prolactin-elevating) with clozapine (prolactin-sparing) in an open, non randomized study (Hummer et al. 1999). Both haloperidol and clozapine were correlated with the same frequency of sexual side effects after six weeks with weekly evaluations. Not in line with other studies these sexual dysfunctions seemed to subside during monthly follow-up in both treatment groups. As the prevalence of sexual dysfunctions in patients treated with antipsychotics for a long time has hardly been studied and the available findings are not consistent we decided to examine sexual side effects in patients who were being treated for more than six months with either classical antipsychotics or clozapine.

Method

In- or out-patients being treated at the University Medical Center Groningen (UMCG) or the Mental Healthcare Foundation Groningen (GGz Groningen) were asked to participate in a study evaluating their experiences with antipsychotics. The study has not been sponsored by any third party and the study design was in agreement with the local ethical commission.

In order to reflect patients having more or less the same severity of illness, only patients treated with depot antipsychotics or clozapine could enter the study. In order to reduce selection bias, all patients who were being treated with depot antipsychotics or clozapine were identified using information of the hospital pharmacy database (GGz Groningen) and information of clinicians (GGz Groningen and UMCG). An independent physician (second author) checked the records of the identified patients for fulfilling inclusion criteria. Inclusion criteria were a diagnosis within the schizophrenia spectrum (schizophreniform disorder, schizophrenia, schizoaffective disorder) age between 18 and 65 years, being

treated with only one antipsychotic, on stable for at least 6 months. Antipsychotics could be either a classical depot antipsychotic or clozapine. No co-medication with known influence on sexual functioning was allowed. Patients had to be able to give oral and written informed consent. Patients were asked to participate by their therapists. Two independent raters performed the interviews and they scheduled appointments with the eligible patients. Both interviewers were trained psychologists. To reduce possible bias of the interviewers, they agreed not to be informed about any study hypothesis.

Socio-demographical information was gathered including diagnosis (information of the treating physician), duration of illness, duration of using antipsychotics and the duration of use of the present antipsychotic and other medication.

The patients were interviewed using the Antipsychotics and Sexual Functioning Questionnaire (ASFQ), an interview based upon the UKU side effects rating scale (Lingjaerde et al. 1987; Knegtering and Castelein 2001). The ASFQ includes semi-structured items assessing improvement or worsening of sexual functioning attributed to the use of antipsychotics. An open question about side effects in general is followed by a semi-structured questioning about libido, orgasm and galactorrhoea, for men erection and ejaculation and for women vaginal lubrication and menstruation.

Statistics

We did pair-wise comparisons to identify possible differences between demographical data and between antipsychotics in inducing sexual side effects. The statistical methods applied were: chi-square tests for pair-wise differences in percentages patients with sexual dysfunction. Two sided t-tests were applied for pair-wise differences in mean age, duration of illness and duration of treatment.

Results

Two hundred patients were selected from the pharmacy database treated with either depot antipsychotics or clozapine for more than six months. After checking the medical files half of these patients had to be excluded for not fulfilling the inclusion criteria for the study (other diagnosis, age, treated with more than one antipsychotic or other co-medication possible influencing sexual functioning like antidepressants or lithium, diabetes mellitus). Thirty patients did not want to participate in the study, 20 patients were considered by their treating physician to be too ill to be interviewed, Fifteen could not be traced or did not show up on their appointment. Finally thirty-five patients (24 men and 11 women) agreed to participate and could be included. Demographical data of these patients as well as numbers of years treated with former and presented antipsychotics are presented in table 7.1

Table 7.1. Demographical data of patients being treated with classical antipsychotics or clozapine for more than 6 months

	Clozapine	Classical (depot) antipsychotics	Statistics evaluating possibly significant differences between the groups
Number of men/women	11/3	13/8	NS
Mean age in years (range)	34.9 (20-44)	44.0 (26-61)	t=-2.888 df=33 p=0.007
Being involved in a partner relationship last year	5/14 (36 %)	6/21 (29%)	NS
Presently having a partner and living together	2/14 (14%)	1/21 (5%)	NS
Having a partner not living together	4/14 (29%)	4/21 (19%)	NS
Never had a partner	8/14 (57%)	14/21 (66%)	NS
Mean number of years treated with antipsychotics (range)	7.3 (2.5-15)	11 (2-25)	t=-1.943 df=33 p=0.64
Mean number of years treated with the present antipsychotic (range)	4.7 (1-8)	5.6 (0.5-15)	NS

In response to the open questions, 3 patients indicated to experience sexual side effects; all treated with classical depot antipsychotics. In response to the semi-structured questions 33% of the interviewed patients on depot antipsychotics and 33% of those using clozapine reported loss of libido. Reduction of the capacity to experience an orgasm and erectile dysfunction were only reported by patients treated with classical antipsychotics (22% and 25% respectively). 11% of patients treated with clozapine and 36% of patients using classical antipsychotics reported a reduction in the volume of ejaculate. There was a trend showing clozapine to be associated with less negative effects on orgasm, erection and ejaculation although this did not reach statistical significance (see table 7.2).

Table 7.2. Sexual dysfunction in men and women treated with long-term depot antipsychotics or clozapine

	Clozapine (N=14)	Classical (depot) (N=21)	Statistics
	Number of patients with complain/patients being able to answer (%)		
Decreased libido (men and women)	4/12 (33%)	6/18 (33%)	Chi-square 0.215 df=1 p=0.64
Decreased orgasm (men and women)	0/12 (0%)	4/18 (22%)	Chi-square 2.836, df=1 p=0.09
Erection	0/9 (0%)	3/12 (25%)	Chi-square 2.625 df=1 p=0.10
Ejaculation	1/9 (11%)	4/11 (36%)	Chi-square 1.111 df=1 p=0.29

In table 7.3 the data of this long-term treatment of antipsychotics are compared with data from other studies performed by our group obtained in patients who were using either classical (oral) antipsychotics or clozapine for six weeks. The details of

these studies are described in chapter 9. Neither classical antipsychotics, nor clozapine showed significant differences regarding the incidence of sexual dysfunctions after six weeks or long-term treatment with the antipsychotics (Chi-square NS).

Table 7.3. Number of patients experiencing sexual dysfunction versus the total number of patients responded on that item and the percentage of patients with a sexual dysfunction attributed to antipsychotic medication

Treatment	Men and women				Men			
	Libido		Orgasm		Erection		Ejaculation	
	6 weeks	long-term	6 weeks	long-term	6 weeks	long-term	6 weeks	Long-term
Classical	15/ 42 (36%)	6/18 (33%)	6/ 37 (16%)	4/18 (22%)	8/29 (28%)	3/12 (25%)	5/25 (20%)	3/12 (25%)
Clozapine	3/ 19 (16%)	4/12 (33%)	1/ 14 (7%)	0/12 (0%)	1/12 (8%)	0/9 (0%)	2/11 (18%)	1/9 (11%)

Discussion and conclusions

We had aimed at an epidemiological representative cross-sectional cohort study comparing patients being treated for at least six months with classical (depot) antipsychotics and clozapine. However we met many problems in including the preferred number of patients. A great number of patients had to be excluded using multiple antipsychotics or other co-medication. A further complication was the significant difference between the long-term treatment groups in mean age. Higher age may be a risk-factor for experiencing more sexual side effects (Smith et al. 2002). Still by excluding patients above 55 years from the database and eliminating the statistical differences in age, did not change the results. In addition to the limitations of this study we could not include enough women to examine their sexual functioning in detail.

Still the findings of this study are in line with previous studies. Only 3 patients (all on classical antipsychotics) reported sexual dysfunctions without explicitly asking for them. This is in line with our former studies, showing that about 10% of patients treated with classical antipsychotics mention sexual side effects spontaneously (Knegtering et al. 1998). In studies using semi-structured questionnaires between 30 to 50% of the patients report a reduction in libido or orgasm after six weeks treatment with classical antipsychotics. The findings in this study are well within these boundaries. This supports the hypothesis that sexual side effects do not subside after continuation of classical antipsychotics. Also the findings in patients treated with clozapine for more than 6 months are in line with earlier findings in patients treated for six weeks. These preliminary results support the hypothesis that sexual side effects do not subside over time, which is in line with the findings of Lingjaerde (Lingjaerde et al. 1987).

The interpretation of the differential effects of classical depot antipsychotics versus clozapine can only be tentative. Although the difference did not reaching statistical significance, patients treated with clozapine may experience less detrimental effects on orgasm, erection and ejaculation.

Libido reduction is known to be caused by schizophrenia itself as well as by antipsychotic drugs. In contrast to orgasm, erection and ejaculation, libido is difficult for the patient to judge or to attribute (Burke et al. 1994). The results from comparing clozapine to classical antipsychotic could support the hypothesis that serum prolactin elevation (classical) antipsychotics may contribute to the occurrence high frequencies of reduction in erection, orgasm and ejaculation. Prolactin sparing antipsychotics, including clozapine, may have a much lower tendency to induce sexual side effects (Kim et al. 2002; Knegtering et al. 2002; Knegtering et al 2003).

These are just preliminary data. A study with more power is likely to report significant differences. Presently this study is being extended in other psychiatric centers in order to include enough patients to confirm these preliminary findings with enough power.

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